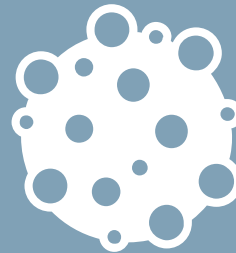




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Estimands in Clinical Trials with Treatment switching

**On behalf of the Treatment Switching Subteam of EFSPi
European Special Interest Group and ASA Scientific
Working Group "Estimands in Oncology"**

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Treatment Switching and Estimands for Overall Survival in Oncology Clinical Trials: Issues and Controversaries

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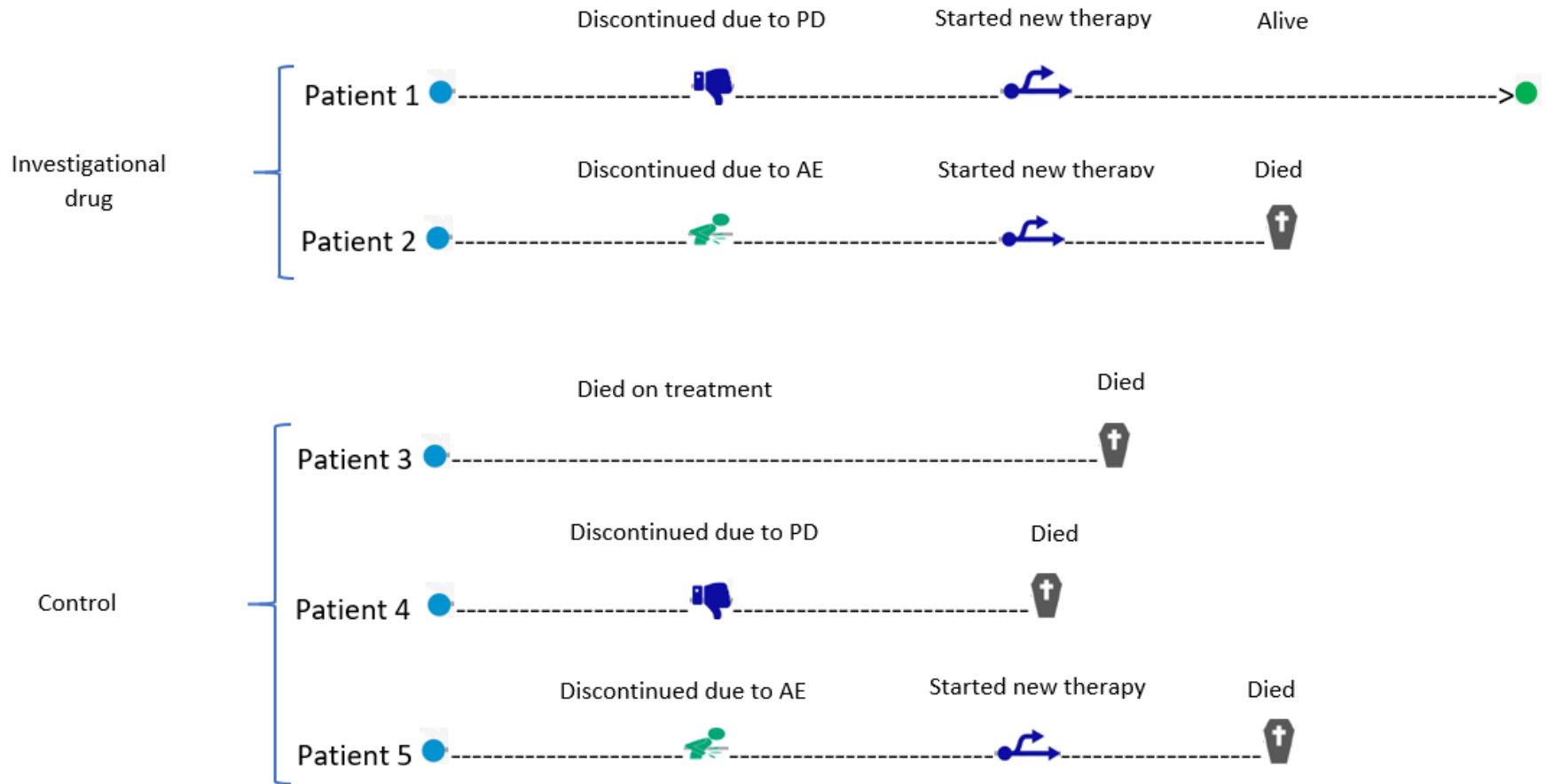
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Introduction

- The need for the **Addendum on Estimands and Sensitivity Analysis in Clinical Trials E9 (R1)** was identified due to recurring issues with a lack of clarity in trial objectives and related treatment effect of interest
- In November 2019, the International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use released an Addendum to E9 guideline on Statistical Principles for Clinical Trials that:
 - Introduced structured framework for clinical trial design
 - Defined intercurrent events, which occur after treatment initiation and affect either the existence or interpretation of the measurement
 - Highlighted the difficulty of assessing treatment effect in the presence of intercurrent events

Potential Journeys of Cancer Patients in Clinical Trials



Potential Journeys of Cancer Patients in Clinical Trials

- Can the prolonged survival be attributed to the investigational drug?
or
- Is it the effect of subsequent therapy?
or
- What would have been the survival of patients one and two had they not received the new therapies?
- What is the key question of interest?
 - Survival regardless of whether a patient received another therapy?
or
 - Survival if patients not received new therapies?

Treatment Switching

- Per E9(R1), subsequent therapy is an intercurrent event
- In oncology, the start of new therapy after study treatment discontinuation or treatment switching is a **key intercurrent event**

Types of Treatment Switching

Description of Treatment Switching	Type of Treatment Switching
From control arm to investigational arm	Crossover*
From control arm to same drug class as investigational arm	Treatment switching
From control or investigational arm to a drug (class) of interest	Treatment switching

* In the time-to-event analysis when crossover occurs in an oncology trial. For example, control patients cross over to the experimental treatment when progression is observed, and the interest is in estimating the hypothetical effect on overall survival (OS) when none of the control patients would have crossed over [EMA/845963/2018].

Strategies to Handle Start of New Therapy

- **Treatment policy strategy**
 - Subsequent therapies reflect clinical practice
- **Hypothetical strategy**
 - Subsequent therapies are not clinical practice or were not received
- **Composite strategy**
 - Subsequent therapy is a part of composite endpoint for the Overall Survival (OS) - not applicable
- **Principal stratum strategy**
 - Prospectively identifying patients who will take subsequent therapy (difficult to predict/not applicable)
- **While on treatment strategy**
 - Considering survival only prior to the subsequent therapy (not applicable)

Strategies to Handle Start of New Therapy

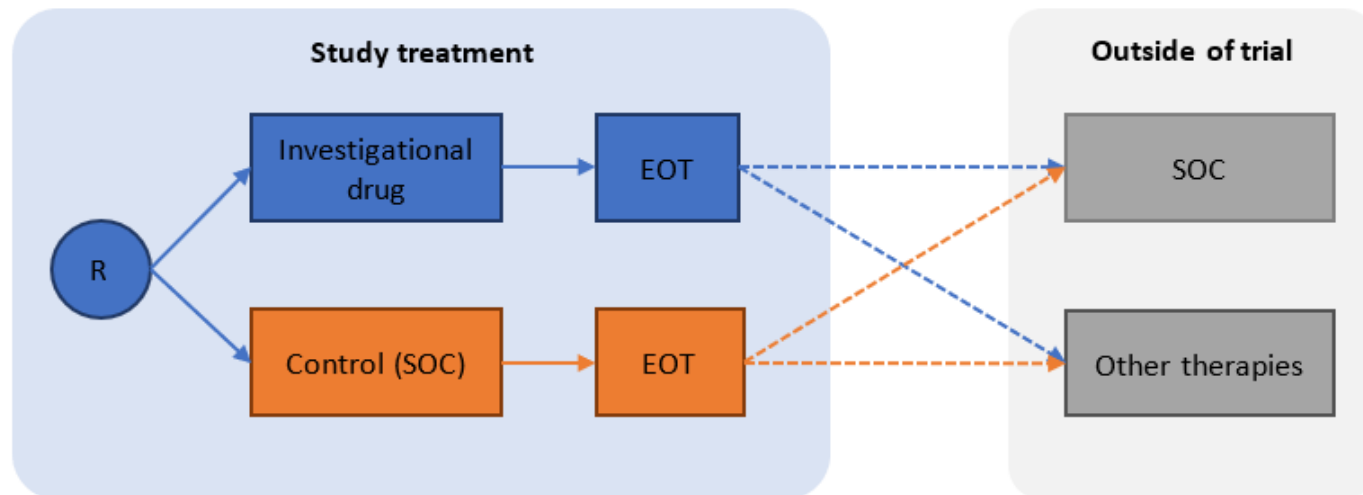
- **Treatment policy strategy question of interest:** Survival benefit of investigational drug regardless of what happens after treatment discontinuation
 - It is assumed that subsequent therapies given after treatment discontinuation reflect clinical practice
 - This strategy corresponds to the Intent-to-Treat (ITT) approach
 - Might be not a meaningful strategy
- **Hypothetical strategy question of interest:** Survival benefit of investigational drug in the hypothetical scenario in which patients do not receive subsequent therapies, i.e., adjusted for the effect of subsequent therapies
 - Often used as supportive post-hoc analysis in oncology trials after observing treatment policy may not be addressing the clinical question of interest

Current Routine Practice and Motivation

- Traditional analysis of OS in the confirmatory study is performed ignoring treatment switching (treatment policy)
- Survival benefit of investigational treatment is likely to be underestimated when control group patients switch more frequently to treatment prolonging OS
- Treatment landscape in oncology is rapidly changing and differs from country to country

Treatment Switching Scenario One

- Investigational drug vs. control; both arms can receive subsequent therapies reflecting clinical practice



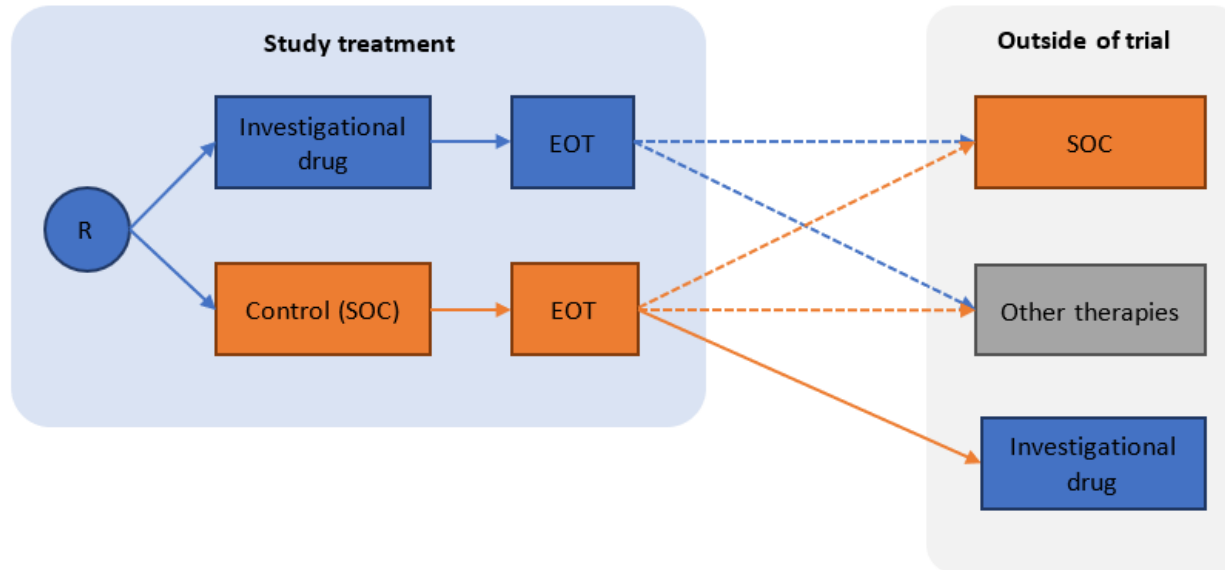
Clinical question of interest:

What is the OS benefit of the investigational drug followed by any subsequent treatments compared to control [standard of care (SOC)] followed by any subsequent therapies? => Treatment policy strategy.

The comparison is between the sequence of investigational drug and other therapies and the sequence of control treatment and other therapies.

Treatment Switching Scenario Two

- Investigational drug vs. control; investigational drug is approved as next-line therapy after SOC

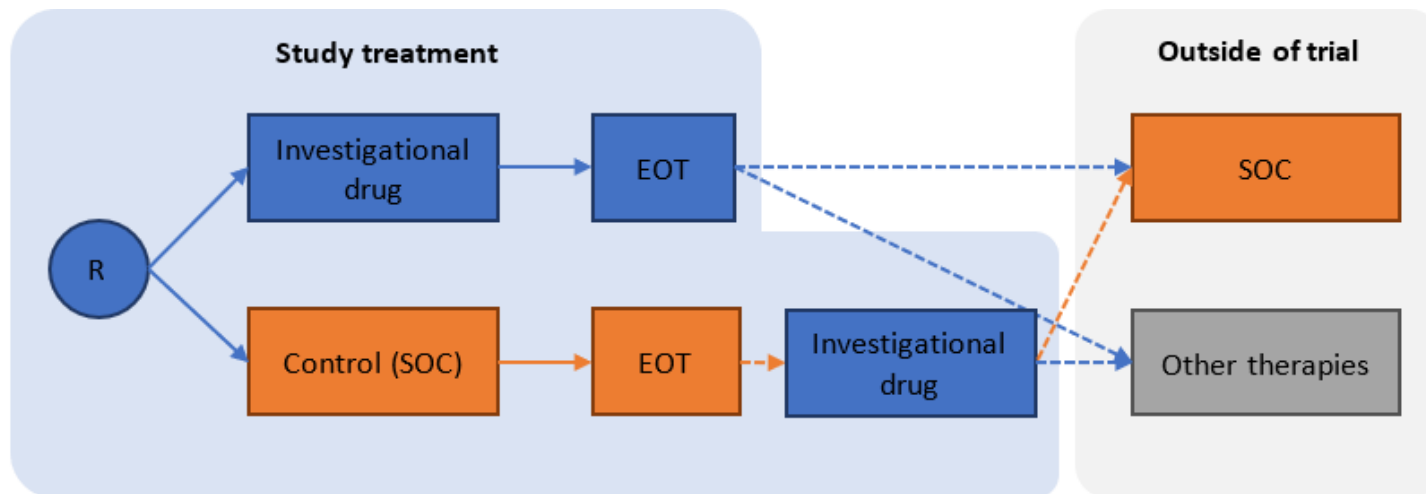


Vast majority of patients switch from control arm => OS benefit due to starting investigational treatment as line X therapy in comparison to starting as line X+1 therapy.

Clinical question of interest: The same as in scenario one.

Treatment Switching Scenario Three

- Investigational drug vs. control with crossover to not-yet-approved investigational drug



The investigational drug is not an approved therapy but has shown promise in early-stage studies and there is a high unmet medical need in the target population. Therefore, it is allowed to switch from the control arm to the investigational drug upon progression.

Clinical question of interest: What is the OS benefit of the investigational drug vs. SOC if cross-over opportunity would not have existed? => Hypothetical strategy could be more informative for clinicians and patients.

Challenges to Select Most Meaningful Strategy

- The scenarios demonstrate the importance of multidisciplinary discussions at study design stage to clarify the scientific question of interest.
- Knowledge of competitive landscape is critical to ensure the main research question regarding OS is identified. SOC's are likely to be different between countries.
- These scenarios are theoretical examples. However, multinational trials can be much more complex. Most trials in oncology will be a mixture of the scenarios.
- Different stakeholders (patients, clinicians, payers, etc.) might define different SOC's for different patient populations within the same trial (e.g., Ibrutinib trial was split into three populations by German GB-A [federal joint committee], according to their definition of appropriate comparator therapies).

Estimand Regardless of Treatment Switching (Treatment Policy)

- Objective is to evaluate OS benefit assuming switching is not associated with survival/covariates.
- The treatment policy estimand is defined as time from randomization to death regardless of treatment changes.
- Analysis method is standard proportional hazards Cox model and is guided by treatment policy strategy to handle treatment switching.
- This estimand may not be clinically relevant due to systematic treatment switching. If switching is associated with survival, then the treatment effect may be underestimated.
- Following Fleming et al. (2009), to maintain the integrity of random assignment, it is recommended to present treatment policy estimand along with other more meaningful estimands.

Estimand for Treatment Switching (Hypothetical Strategy with IPCW)

- Estimand that evaluates the OS benefit adjusted for treatment switching is defined as the time from randomization to death, while the start of any subsequent therapy before death is handled by hypothetical strategy.
- Analysis method is Cox model with inverse probability censoring weighting (IPCW) (Robins JM et al., 2000).
- IPCW assumes that “patients who do not switch serve as proxies for those who do.” Informative censoring introduced by censoring at treatment switching is adjusted by weighting remaining observations using baseline and time-dependent covariates.
- Key assumption: no unmeasured confounders.

Estimands for Crossover (Hypothetical Strategy with RPSFT)

- Estimand that evaluates OS benefit adjusted for treatment crossover is defined as the time from randomization to death and the intercurrent event of crossover is handled by hypothetical strategy.
- Analysis method is Cox model with counterfactual survival times for crossover patients from rank preserving structural failure time (RPSFT) approach (Robins JM et al., 1991; Branson M et al., 2002).
- RPSFT refers to a model-based approach that adjusts the survival time of patients, who switch from the control arm to the investigational arm.

Estimands for Crossover at Progression (Hypothetical Strategy with Two-Stage Method)

- Estimand that evaluates OS benefit adjusted for treatment crossover at a specific disease-related time point, typically progression, and the survival time after progression is adjusted using hypothetical strategy.
- Analysis method is based on reconstructed survival times obtained by the two-stage approach (Latimer NR et al. 2014).
- The two-stage approach defines a secondary baseline by a specific disease-related time point, e.g., progression, at which crossover is possible.
- Secondary baseline requires complete data collection of the disease-related time point. It also assumes switching occurs soon after that time. Another assumption is about no unobserved confounders at the secondary baseline.

Summary

- Standard practice should be to account for treatment switching in the analysis during the planning stage of the trial to incorporate that into design and data collection strategies.
- Estimand where treatment switching is handled with treatment policy is meaningful in most situations and is appropriate if subsequent therapies reflect clinical practice.
- In situations when subsequent therapies do not reflect clinical practice, other estimands handling treatment switching with hypothetical strategy are more versatile.
- Other than hypothetical strategies, principal stratum or composite strategies could be considered to handle intercurrent event of treatment switching.

References

- Branson M., Whitehead J. (2002). *Estimating a treatment effect in survival studies in which patients switch treatment*. Statistics in Medicine, 2002 September 15, 21(17), 2449-2463.
- Fleming T.R., Rothmann M.D., Lu H.L. (2009). *Issues in Using Progression-Free Survival When Evaluating Oncology Products*. Journal of Clinical Oncology 2009 June 10, 27(17), 2874-2880, doi: 10.1200/JCO.2008.20.4107.
- Latimer NR, Abrams KR, Lambert PC, Crowther MJ, Wailoo AJ, Morden JP, et al. *Adjusting for treatment switching in randomised controlled trials – a simulation study and a simplified two-stage method*. Stat Methods Med Res 2014;0962280214557578 [EPub ahead of print].
- Robins J. M., Finkelstein D. M. (2000). *Correcting for noncompliance and dependent censoring in an AIDS Clinical Trial with inverse probability of censoring weighted (IPCW) log-rank tests*. Biometrics, September 2000, 56(3), 779-788.
- Robins J. M., Tsiatis A. A. (1991). *Correcting for noncompliance in randomized trials using rank preserving structural failure time models*. Communication in Statistics - Theory and Methods, 1991, 20(8), 2609-2631.
- EMA/845963/2018, Human Medicines Research and Development Support Division Question and answer on adjustment for cross-over in estimating effects in oncology trials.

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